

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Sandostatin LAR safely and effectively. See full prescribing information for Sandostatin LAR.

Sandostatin LAR[®] Depot (octreotide acetate for injectable suspension)
Initial U.S. Approval: 1988

INDICATIONS AND USAGE

Sandostatin LAR is a somatostatin analogue indicated for:
Treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous injection for:

- Acromegaly (1.1)
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors (1.2)
- Profuse watery diarrhea associated with VIP-secreting tumors (1.3)

DOSAGE AND ADMINISTRATION

Patients not currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 50 mcg three times daily Sandostatin Injection subcutaneously for 2 weeks followed by Sandostatin LAR 20 mg intragluteally every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: Sandostatin Injection subcutaneously 100-600 mcg/day in 2-4 divided doses for 2 weeks followed by Sandostatin LAR 20 mg every 4 weeks for 2 months (2.2)

Patients currently receiving Sandostatin Injection subcutaneously:

- Acromegaly: 20 mg every 4 weeks for 3 months (2.1)
- Carcinoid Tumors and VIPomas: 20 mg every 4 weeks for 2 months (2.2)

Renal Impairment, patients on dialysis: 10 mg every 4 weeks (2.3)

Hepatic Impairment, patients with cirrhosis: 10 mg every 4 weeks (2.4)

DOSAGE FORMS AND STRENGTHS

Vials: 10 mg per 5 mL, 20 mg per 5 mL or 30 mg per 5 mL (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Gallbladder abnormalities may occur. Monitor periodically. (5.1)
- Glucose Metabolism: Hypoglycemia or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment may need adjustment. (5.2)
- Thyroid Function: Hypothyroidism may occur. Monitor thyroid levels periodically. (5.3)
- Cardiac Function: Bradycardia, arrhythmia or conduction abnormalities may occur. Use with caution in at-risk patients. (5.4)

ADVERSE REACTIONS

The most common adverse reactions, occurring in $\geq 20\%$ of patients are:

- Acromegaly: diarrhea, cholelithiasis, abdominal pain, flatulence (6.1)
- Carcinoid Syndrome: back pain, fatigue, headache, abdominal pain, nausea, dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

The following drugs require monitoring and possible dose adjustment when used with Sandostatin LAR: cyclosporine, insulin, oral hypoglycemic agents, beta-blockers, bromocriptine (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

1 INDICATIONS AND USAGE

- 1.1 Acromegaly
- 1.2 Carcinoid Tumors
- 1.3 Vasoactive Intestinal Peptide Tumors (VIPomas)
- 1.4 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Acromegaly
- 2.2 Carcinoid Tumors and VIPomas
- 2.3 Special Populations: Renal Impairment
- 2.4 Special Populations: Hepatic Impairment – Cirrhotic Patients

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Cholelithiasis and Gallbladder Sludge
- 5.2 Hyperglycemia and Hypoglycemia
- 5.3 Thyroid Function Abnormalities
- 5.4 Cardiac Function Abnormalities
- 5.5 Nutrition
- 5.6 Monitoring: Laboratory Tests
- 5.7 Drug Interactions

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
 - 6.1.1 Acromegaly
 - 6.1.2 Carcinoid and VIPomas
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Cyclosporine

- 7.2 Insulin and Oral Hypoglycemic Drugs

- 7.3 Bromocriptine

- 7.4 Other Concomitant Drug Therapy

- 7.5 Drug Metabolism Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- 8.3 Nursing Mothers

- 8.4 Pediatric Use

- 8.5 Geriatric Use

- 8.6 Renal Impairment

- 8.7 Hepatic Impairment - Cirrhotic Patients

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

- 12.2 Pharmacodynamics

- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- 13.2 Reproductive Toxicology Studies

14 CLINICAL STUDIES

- 14.1 Acromegaly

- 14.2 Carcinoid Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sandostatin LAR Depot 10 mg, 20 mg and 30 mg is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

1.1 Acromegaly

Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal [see *Clinical Studies (14)* and *Dosage and Administration (2)*].

1.2 Carcinoid Tumors

Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

1.3 Vasoactive Intestinal Peptide Tumors (VIPomas)

Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.4 Important Limitations of Use

In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

2 DOSAGE AND ADMINISTRATION

- Sandostatin LAR Depot should be administered by a trained health care provider. It is important to closely follow the mixing instructions included in the packaging. Sandostatin LAR Depot must be administered immediately after mixing.

- **Do not directly inject diluent without preparing suspension.**

- Sandostatin LAR Depot should be administered intragluteally at 4-week intervals. Administration of Sandostatin LAR Depot at intervals greater than 4 weeks is not recommended.

- Injection sites should be rotated in a systematic manner to avoid irritation. Deltoid injections should be avoided due to significant discomfort at the injection site when given in that area.

- **Sandostatin LAR Depot should never be administered intravenously or subcutaneously.**

The following dosage regimens are recommended.

2.1 Acromegaly

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously in an initial dose of 50 mcg three times daily which may be titrated. Most patients require doses of 100 mcg to 200 mcg three times daily for maximum effect but some patients require up to 500 mcg three times daily.

Patients should be maintained on Sandostatin Injection subcutaneous for at least 2 weeks to determine tolerance to octreotide. Patients who are considered to be “responders” to the drug, based on GH and IGF-1 levels and who tolerate the drug can then be switched to Sandostatin LAR Depot in the dosage scheme described below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched directly to Sandostatin LAR Depot in a dose of 20 mg given IM intragluteally at 4-week intervals for 3 months. After 3 months, dosage may be adjusted as follows:

- GH ≤ 2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: maintain Sandostatin LAR Depot dosage at 20 mg every 4 weeks.
- GH > 2.5 ng/mL, IGF-1 elevated, and/or clinical symptoms uncontrolled, increase Sandostatin LAR Depot dosage to 30 mg every 4 weeks.
- GH ≤ 1 ng/mL, IGF-1 normal and clinical symptoms controlled, reduce Sandostatin LAR Depot dosage to 10 mg every 4 weeks.
- If GH, IGF-1, or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks. Doses higher than 40 mg are not recommended.

In patients who have received pituitary irradiation, Sandostatin LAR Depot should be withdrawn yearly for approximately 8 weeks to assess disease activity. If GH or IGF-1 levels increase and signs and symptoms recur, Sandostatin LAR Depot therapy may be resumed.

2.2 Carcinoid Tumors and VIPomas

Patients Not Currently Receiving Octreotide Acetate

Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously. The suggested daily dosage for carcinoid tumors during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). Some patients may require doses up to 1500 mcg/day. The suggested daily dosage for VIPomas is 200-300 mcg in 2-4 divided doses (range 150-750 mcg); dosage may be adjusted on an individual basis to control symptoms but usually doses above 450 mcg/day are not required.

Sandostatin Injection should be continued for at least 2 weeks. Thereafter, patients who are considered “responders” to octreotide acetate and who tolerate the drug may be switched to Sandostatin LAR Depot in the dosage regimen as described below (Patients Currently Receiving Sandostatin Injection).

Patients Currently Receiving Sandostatin Injection

Patients currently receiving Sandostatin Injection can be switched to Sandostatin LAR Depot in a dosage of 20 mg given IM intragluteally at 4-week intervals for 2 months. Because of the need for serum octreotide to reach therapeutically effective levels following initial injection of Sandostatin LAR Depot, carcinoid tumor and VIPoma patients should continue to receive Sandostatin Injection subcutaneously for at least 2 weeks in the same dosage they were taking before the switch. Failure to continue subcutaneous injections for this period may result in exacerbation of symptoms. (Some patients may require 3 or 4 weeks of such therapy.)

After 2 months, dosage may be adjusted as follows:

- If symptoms are adequately controlled, consider a dose reduction to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks. Many patients can, however, be satisfactorily maintained at a 10-mg dosage every 4 weeks.
- If symptoms are not adequately controlled, increase Sandostatin LAR Depot to 30 mg every 4 weeks if symptoms are not adequately controlled. Patients who achieve good control on a 20-mg dose may have their dose lowered to 10 mg for a trial period. If symptoms recur, dosage should then be increased to 20 mg every 4 weeks.
- Dosages higher than 30 mg are not recommended.

Despite good overall control of symptoms, patients with carcinoid tumors and VIPomas often experience periodic exacerbation of symptoms (regardless of whether they are being maintained on Sandostatin Injection or Sandostatin LAR Depot). During these periods they may be given Sandostatin Injection subcutaneously for a few days at the dosage they were receiving prior to switching to Sandostatin LAR Depot. When symptoms are again controlled, the Sandostatin Injection subcutaneous can be discontinued.

2.3 Special Populations: Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg every 4 weeks. In other patients with renal impairment, the starting dose should be similar to a nonrenal patient (i.e., 20 mg every 4 weeks) [*see Clinical Pharmacology (12)*].

2.4 Special Populations: Hepatic Impairment – Cirrhotic Patients

In patients with established cirrhosis of the liver, the starting dose should be 10 mg every 4 weeks [*see Clinical Pharmacology (12)*].

3 DOSAGE FORMS AND STRENGTHS

Sandostatin LAR Depot is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg, or 30 mg strength, a syringe containing 2.5 mL of diluent, two sterile 1½” 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Sandostatin may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Patients should be monitored periodically [*see Adverse Reactions (6)*].

5.2 Hyperglycemia and Hypoglycemia

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when Sandostatin LAR treatment is initiated, or when the dose is altered. Antidiabetic treatment should be adjusted accordingly [*see Adverse Reactions (6)*].

5.3 Thyroid Function Abnormalities

Octreotide suppresses the secretion of thyroid-stimulating hormone, which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total and/or free T₄) is recommended during chronic octreotide therapy [*see Adverse Reactions (6)*].

5.4 Cardiac Function Abnormalities

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and nonspecific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge [*see Adverse Reactions (6)*].

5.5 Nutrition

Octreotide may alter absorption of dietary fats.

Depressed vitamin B₁₂ levels and abnormal Schilling tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B₁₂ levels is recommended during therapy with Sandostatin LAR Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

5.6 Monitoring: Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy [*see Dosage and Administration (2.0)*].

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide) baseline and periodic total and/or free T₄ measurements should be performed during chronic therapy

5.7 Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine [*see Drug Interactions (7.2)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

6.1.1 Acromegaly

The safety of Sandostatin LAR in the treatment of acromegaly has been evaluated in three phase 3 studies in 261 patients, including 209 exposed for 48 weeks and 96 exposed for greater than 108 weeks. Sandostatin LAR was studied primarily in a double-blind, cross-over manner. Patients on subcutaneous Sandostatin Injection were switched to the LAR formulation followed by an open-label extension. The population age range was 14-81 years old and 53% were female. Approximately 35% of these acromegaly patients had not been treated with surgery and/or radiation. Most patients received a starting dose of 20 mg every 4 weeks intramuscularly. Dose was up or down titrated based on efficacy and tolerability to a final dose between 10-60 mg every 4 weeks. Table 1 below reflects adverse events from these studies regardless of presumed causality to study drug.

Table 1. Adverse Events Occurring in ≥10% of Acromegalic Patients in the Phase 3 Studies

WHO Preferred Term	Phase 3 Studies (Pooled)
	Number (%) of Subjects with AE's
	10 mg/20 mg/30 mg
	(n=261) n (%)
Diarrhea	93 (35.6)
Abdominal Pain	75 (28.7)
Flatulence	66 (25.3)
Influenza-Like Symptoms	52 (19.9)
Constipation	46 (17.6)
Headache	40 (15.3)
Anemia	40 (15.3)
Injection Site Pain	36 (13.8)
Cholelithiasis	35 (13.4)
Hypertension	33 (12.6)
Dizziness	30 (11.5)
Fatigue	29 (11.1)

The safety of Sandostatin LAR in the treatment of acromegaly was also evaluated in a postmarketing randomized phase 4 study. 104 patients were randomized to either pituitary surgery or 20 mg of Sandostatin LAR. All the patients were treatment naïve ('de novo'). Crossover was allowed according to treatment response and a total of 76 patients were exposed to Sandostatin LAR. Approximately half of the patients initially randomized to Sandostatin LAR were exposed to Sandostatin LAR up to 1 year. The population age range was between 20-76 years old and 45% were female, 93% were Caucasian, and 1% Black. The majority of these patients were exposed to 30 mg every 4 weeks. Table 2 below reflects the adverse events occurring in this study regardless of presumed causality to study drug.

Table 2. Adverse Events Occurring in ≥10% of Acromegalic Patients in Phase 4 Study

WHO Preferred Term	Phase 4 Study	Phase 4 Study
	SAS LAR	Surgery
	N=76	N=64
	n (%)	n (%)
Diarrhea	36 (47.4)	2 (3.1)
Cholelithiasis	29 (38.2)	3 (4.7)
Abdominal Pain	19 (25.0)	2 (3.1)
Nausea	12 (15.8)	5 (7.8)
Alopecia	10 (13.2)	5 (7.8)
Injection Site Pain	9 (11.8)	0
Abdominal Pain Upper	8 (10.5)	0
Headache	8 (10.5)	6 (9.4)
Epistaxis	0	7 (10.9)

Gallbladder Abnormalities

Single doses of Sandostatin Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex, or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge, and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In acromegaly patients treated with either Sandostatin Injection or Sandostatin LAR Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients [see *Warnings and Precautions* (5)].

Hypothyroidism

In acromegaly patients receiving Sandostatin Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin Injection. In acromegalics treated with Sandostatin LAR Depot, hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR Depot required initiation of thyroid hormone replacement therapy [see *Warnings and Precautions* (5)].

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin Injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see *Warnings and Precautions* (5)].

Gastrointestinal

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 3.

Table 3. Number (%) of Acromegalic Patients with Common G.I. Adverse Events

Adverse Event	Sandostatin Injection S.C. Three Times Daily n=114		Sandostatin LAR Depot Every 28 Days n=261	
	n	%	n	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Nausea	34	(29.8)	27	(10.3)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Vomiting	5	(4.4)	17	(6.5)

Only 2.6% of the patients on Sandostatin Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR Depot, the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances, gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Pain at the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg, and 30 mg, respectively, of Sandostatin LAR Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Antibodies to Octreotide

Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR Depot.

6.1.2 Carcinoid and VIPomas

The safety of Sandostatin LAR in the treatment of carcinoid tumors and VIPomas has been evaluated in one phase 3 study. Study 1 randomized 93 patients with carcinoid syndrome to Sandostatin LAR 10 mg, 20 mg, or 30 mg in a blind fashion or to open-label Sandostatin Injection subcutaneously. The population age range was between 25-78 years old and 44% were female, 95% were Caucasian and 3% Black. All the patients had symptom control on their previous Sandostatin subcutaneous treatment. 80 patients finished the initial 24 weeks of Sandostatin exposure in Study 1. In Study 1, comparable numbers of patients were randomized to each dose. Table 4 below reflects the adverse events occurring in >15% of patients regardless of presumed causality to study drug.

Table 4. Adverse Events Occurring in ≥15% of Carcinoid Tumor and VIPoma Patients in Study 1

WHO Preferred Term	Number (%) of Subjects with AE's (n=93)			
	Sc N=26	10 mg N=22	20 mg N=20	30 mg N=25
Abdominal Pain	8 (30.8)	8 (35.4)	2 (10.0)	5 (20.0)
Arthropathy	5 (19.2)	2 (9.1)	3 (15.0)	2 (8.0)
Back Pain	7 (26.9)	6 (27.3)	2 (10.0)	2 (8.0)
Dizziness	4 (15.4)	4 (18.2)	4 (20.0)	5 (20.0)
Fatigue	3 (11.5)	7 (31.8)	2 (10.0)	2 (8.0)
Flatulence	3 (11.5)	2 (9.1)	2 (10.0)	4 (16.0)
Generalized Pain	4 (15.4)	2 (9.1)	3 (15.0)	1 (4.0)
Headache	5 (19.2)	4 (18.2)	6 (30.0)	4 (16.0)
Musculoskeletal Pain	4 (15.4)	0	1 (5.0)	0
Myalgia	0	4 (18.2)	1 (5.0)	1 (4.0)
Nausea	8 (30.8)	9 (40.9)	6 (30.0)	6 (24.0)
Pruritus	0	4 (18.2)	0	0
Rash	1 (3.8)	0	3 (15.0)	0
Sinusitis	4 (15.4)	0	1 (5.0)	3 (12.0)
URTI	6 (23.1)	4 (18.2)	2 (10.0)	3 (12.0)
Vomiting	3 (11.5)	0	0	4 (16.0)

Gallbladder Abnormalities

In clinical trials, 62% of malignant carcinoid patients who received Sandostatin LAR Depot for up to 18 months developed new biliary abnormalities including jaundice, gallstones, sludge, and dilatation. New gallstones occurred in a total of 24% of patients.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot [see *Warnings and Precautions* (5)].

Hypothyroidism

In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported [see *Warnings and Precautions* (5)].

Cardiac

Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. In carcinoid syndrome patients, sinus bradycardia developed in 19%, conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see *Warnings and Precautions* (5)].

Other Clinical Studies Adverse Events

Other clinically significant adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving Sandostatin LAR Depot were malignant hyperpyrexia, cerebral vascular disorder, rectal bleeding, ascites, pulmonary embolism, pneumonia and pleural effusion.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the postapproval use of Sandostatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial infarction has been observed in the postmarketing setting, mainly in patients with cardiovascular risk factors.

Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the postmarketing setting include anaphylactoid reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paresis, deafness, visual field defect, aphasia, scotoma, status asthmaticus, pulmonary hypertension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pituitary apoplexy, breast carcinoma, suicide attempt, paranoia, migraines, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud's syndrome, glaucoma, pulmonary nodule, pneumothorax aggravated, cellulitis, Bell's palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyp, fatty liver, abdomen enlarged, libido decrease, and petechiae.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

7.2 Insulin and Oral Hypoglycemic Drugs

Octreotide inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when Sandostatin LAR treatment is initiated or when the dose is altered and antidiabetic treatment should be adjusted accordingly.

7.3 Bromocriptine

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.

7.4 Other Concomitant Drug Therapy

Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with octreotide. Dose adjustments of concomitant medication may be necessary.

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.

7.5 Drug Metabolism Interactions

Limited published data indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose and have revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [see *Nonclinical Toxicology* (13.2)].

8.3 Nursing Mothers

It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Sandostatin LAR Depot is administered to a nursing woman.

8.4 Pediatric Use

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40 mg Sandostatin LAR Depot administered by IM injection every 4 weeks was approximately 3 ng/mL. Steady-state concentration was achieved after 3 injections of a 40-mg dose.

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo-controlled 6-month study in 60 pediatric patients age 6-17 years with hypothalamic obesity resulting from cranial insult. Mean BMI increased 0.1 kg/m² in Sandostatin LAR Depot-treated subjects compared to 0.0 kg/m² in saline control-treated subjects. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot

40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10-30 mg once a month.

8.5 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. In patients with mild, moderate, or severe renal impairment there is no need to adjust the starting dose of Sandostatin. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in nonrenal patients [see *Clinical Pharmacology* (12)].

8.7 Hepatic Impairment - Cirrhotic Patients

In patients with established liver cirrhosis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. Once at a higher dose, patient should be maintained or dose adjusted based on response and tolerability as in any noncirrhotic patients [see *Clinical Pharmacology* (12)].

10 OVERDOSAGE

No frank overdose has occurred in any patient to date. Sandostatin Injection given in intravenous bolus doses of 1 mg (1000 mcg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 mcg) given intravenously over 20 minutes and of 120 mg (120,000 mcg) given intravenously over 8 hours to research patients. Doses of 2.5 mg (2500 mcg) of Sandostatin Injection subcutaneously have, however, caused hypoglycemia, flushing, dizziness, and nausea.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center.

Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference^{®**}.

Mortality occurred in mice and rats given 72 mg/kg and 18 mg/kg intravenously, respectively, of octreotide.

11 DESCRIPTION

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1- (hydroxy-methyl) propyl]-, cyclic (2#7)-disulfide; [R-(R*,R*)].

Sandostatin LAR Depot is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Sandostatin LAR Depot is available as: sterile 5-mL vials in 3 strengths delivering 10 mg, 20 mg, or 30 mg octreotide-free peptide.

Each vial of Sandostatin LAR Depot delivers:

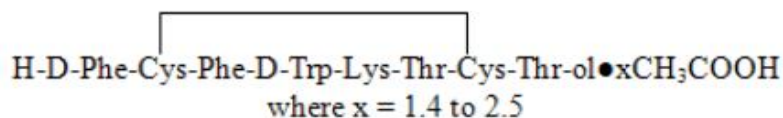
Name of Ingredient	10 mg	20 mg	30 mg
octreotide acetate	11.2 mg*	22.4 mg*	33.6 mg*
D, L-lactic and glycolic acids copolymer	188.8 mg	377.6 mg	566.4 mg
mannitol	41.0 mg	81.9 mg	122.9 mg

*Equivalent to 10/20/30 mg octreotide base.

Each syringe of diluent contains:

carboxymethylcellulose sodium	12.5 mg
mannitol	15.0 mg
water for injection	2.5 mL

The molecular weight of octreotide is 1019.3 (free peptide, C₄₉H₆₆N₁₀O₁₀S₂) and its amino acid sequence is



12 CLINICAL PHARMACOLOGY

Sandostatin LAR Depot is a long-acting dosage form consisting of microspheres of the biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer, containing octreotide. It maintains all of the clinical and pharmacological characteristics of the immediate-release dosage form Sandostatin Injection with the added feature of slow release of octreotide from the site of injection, reducing the need for frequent administration. This slow release occurs as the polymer biodegrades, primarily through hydrolysis. Sandostatin LAR Depot is designed to be injected intramuscularly (intragluteally) once every 4 weeks.

12.1 Mechanism of Action

Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. By virtue of these pharmacological actions, octreotide has been used to treat the symptoms associated with metastatic carcinoid tumors (flushing and diarrhea), and Vasoactive Intestinal Peptide (VIP) secreting adenomas (watery diarrhea).

12.2 Pharmacodynamics

Octreotide substantially reduces and in many cases can normalize growth hormone and/or IGF-1 (somatomedin C) levels in patients with acromegaly.

Single doses of Sandostatin Injection given subcutaneously have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials, the incidence of gallstone or biliary sludge formation was markedly increased [see *Warnings and Precautions* (5)].

Octreotide may cause clinically significant suppression of thyroid-stimulating hormone (TSH).

12.3 Pharmacokinetics

Sandostatin Injection

According to data obtained with the immediate-release formulation, Sandostatin Injection solution, after subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100-mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area-under-the-curve values were dose proportional both after subcutaneous or intravenous single doses up to 400 mcg and with multiple doses of 200 mcg three times daily (600 mcg/day). Clearance was reduced by about 66% suggesting nonlinear kinetics of the drug at daily doses of 600 mcg/day compared to 150 mcg/day. The relative decrease in clearance with doses above 600 mcg/day is not defined.

In healthy volunteers, the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2} = 0.2$ h), the volume of distribution (V_{dss}) was estimated to be 13.6 L and the total body clearance was 10 L/h.

In blood, the distribution of octreotide into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin.

The elimination of octreotide from plasma had an apparent half-life of 1.7 hours, compared with the 1-3 minutes with the natural hormone, somatostatin. The duration of action of subcutaneously administered Sandostatin Injection solution is variable but extends up to 12 hours depending upon the type of tumor, necessitating multiple daily dosing with this immediate-release dosage form. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100-mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (V_{dss}) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals.

The half-life in renal-impaired patients was slightly longer than normal subjects (2.4-3.1 h versus 1.9 h). The clearance in renal-impaired patients was 7.3-8.8 L/h as compared to 8.3 L/h in healthy subjects. In patients with severe renal failure requiring dialysis, clearance was reduced to about half that found in healthy subjects (from approximately 10 L/h to 4.5 L/h).

Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide half-life increasing to 3.7 h and total body clearance decreasing to 5.9 L/h, whereas patients with fatty liver disease showed half-life increasing to 3.4 h and total body clearance of 8.4 L/h. In normal subjects, octreotide half-life is 1.9 h and the clearance is 8.3 L/h which is comparable with the clearance in fatty-liver patients.

Sandostatin LAR Depot

The magnitude and duration of octreotide serum concentrations after an intramuscular injection of the long-acting depot formulation Sandostatin LAR Depot reflect the release of drug from the microsphere polymer matrix. Drug release is governed by the slow biodegradation of the microspheres in the muscle, but once present in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties which are as follows.

After a single IM injection of the long-acting depot dosage form Sandostatin LAR Depot in healthy volunteer subjects, the serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 hour after administration progressively declining over the following 3-5 days to a nadir of <0.01 ng/mL/mg, then slowly increasing and reaching a plateau about 2-3 weeks postinjection. Plateau concentrations were maintained over a period of nearly 2-3 weeks, showing dose proportional peak

concentrations of about 0.07 ng/mL/mg. After about 6 weeks postinjection, octreotide concentration slowly decreased, to <0.01 ng/mL/mg by Weeks 12 to 13, concomitant with the terminal degradation phase of the polymer matrix of the dosage form. The relative bioavailability of the long-acting release Sandostatin LAR Depot compared to immediate-release Sandostatin Injection solution given subcutaneously was 60%-63%.

In patients with acromegaly, the octreotide concentrations after single doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR Depot were dose proportional. The transient Day 1 peak, amounting to 0.3 ng/mL, 0.8 ng/mL, and 1.3 ng/mL, respectively, was followed by plateau concentrations of 0.5 ng/mL, 1.3 ng/mL, and 2.0 ng/mL, respectively, achieved about 3 weeks postinjection. These plateau concentrations were maintained for nearly 2 weeks.

Following multiple doses of Sandostatin LAR Depot given every 4 weeks, steady-state octreotide serum concentrations were achieved after the third injection. Concentrations were dose proportional and higher by a factor of approximately 1.6 to 2.0 compared to the concentrations after a single dose. The steady-state octreotide concentrations were 1.2 ng/mL and 2.1 ng/mL, respectively, at trough and 1.6 ng/mL and 2.6 ng/mL, respectively, at peak with 20 mg and 30 mg Sandostatin LAR Depot given every 4 weeks. No accumulation of octreotide beyond that expected from the overlapping release profiles occurred over a duration of up to 28 monthly injections of Sandostatin LAR Depot. With the long-acting depot formulation Sandostatin LAR Depot administered IM every 4 weeks the peak-to-trough variation in octreotide concentrations ranged from 44%-68%, compared to the 163%-209% variation encountered with the daily subcutaneous three times daily regimen of Sandostatin Injection solution.

In patients with carcinoid tumors, the mean octreotide concentrations after 6 doses of 10 mg, 20 mg, and 30 mg Sandostatin LAR Depot administered by IM injection every 4 weeks were 1.2 ng/mL, 2.5 ng/mL, and 4.2 ng/mL, respectively. Concentrations were dose proportional and steady-state concentrations were reached after 2 injections of 20 mg and 30 mg and after 3 injections of 10 mg.

Sandostatin LAR Depot has not been studied in patients with renal impairment.

Sandostatin LAR Depot has not been studied in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in laboratory animals have demonstrated no mutagenic potential of Sandostatin. No mutagenic potential of the polymeric carrier in Sandostatin LAR Depot, D,L-lactic and glycolic acids copolymer, was observed in the Ames mutagenicity test.

No carcinogenic potential was demonstrated in mice treated subcutaneously with octreotide for 85-99 weeks at doses up to 2000 mcg/kg/day (8x the human exposure based on body surface area). In a 116-week subcutaneous study in rats administered octreotide, a 27% and 12% incidence of injection site sarcomas or squamous cell carcinomas was observed in males and females, respectively, at the highest dose level of 1250 mcg/kg/day (10x the human exposure based on body surface area) compared to an incidence of 8%-10% in the vehicle-control groups. The increased incidence of injection site tumors was most probably caused by irritation and the high sensitivity of the rat to repeated subcutaneous injections at the same site. Rotating injection sites would prevent chronic irritation in humans. There have been no reports of injection site tumors in patients treated with Sandostatin Injection for at least 5 years. There was also a 15% incidence of uterine adenocarcinomas in the 1250 mcg/kg/day females compared to 7% in the saline-control females and 0% in the vehicle-control females. The presence of endometritis coupled with the absence of corpora lutea, the reduction in mammary fibroadenomas, and the presence of uterine dilatation suggest that the uterine tumors were associated with estrogen dominance in the aged female rats which does not occur in humans.

Octreotide did not impair fertility in rats at doses up to 1000 mcg/kg/day, which represents 7x the human exposure based on body surface area.

13.2 Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 16x the highest recommended human dose based on body surface area and have revealed no evidence of harm to the fetus due to octreotide.

14 CLINICAL STUDIES

14.1 Acromegaly

The clinical trials of Sandostatin LAR Depot were performed in patients who had been receiving Sandostatin Injection for a period of weeks to as long as 10 years. The acromegaly studies with Sandostatin LAR Depot described below were performed in patients who achieved GH levels of <10 ng/mL (and, in most cases <5 ng/mL) while on subcutaneous Sandostatin Injection. However, some patients enrolled were partial responders to subcutaneous Sandostatin Injection, i.e., GH levels were reduced by >50% on subcutaneous Sandostatin Injection compared to the untreated state, although not suppressed to <5 ng/mL.

Sandostatin LAR Depot was evaluated in three clinical trials in acromegalic patients.

In two of the clinical trials, a total of 101 patients were entered who had, in most cases, achieved a GH level <5 ng/mL on Sandostatin Injection given in doses of 100 mcg or 200 mcg three times daily. Most patients were switched to 20 mg or 30 mg doses of Sandostatin LAR Depot given once every 4 weeks for up to 27 to 28 injections. A few patients received doses of 10 mg and a few required doses of 40 mg. Growth hormone and IGF-1 levels were at least as well controlled with Sandostatin LAR Depot as they had been on Sandostatin Injection and this level of control remained for the entire duration of the trials.

A third trial was a 12-month study that enrolled 151 patients who had a GH level <10 ng/mL after treatment with Sandostatin Injection (most had levels <5 ng/mL). The starting dose of Sandostatin LAR Depot was 20 mg every 4 weeks for 3 doses. Thereafter, patients received 10 mg, 20 mg or 30 mg every 4 weeks, depending upon the degree of GH suppression [see *Dosage and Administration* (2)]. Growth hormone and IGF-1 were at least as well controlled on Sandostatin LAR Depot as they had been on Sandostatin Injection.

Table 5 summarizes the data on hormonal control (GH and IGF-1) for those patients in the first two clinical trials who received all 27 to 28 injections of Sandostatin LAR Depot.

Table 5. Hormonal Response in Acromegalic Patients Receiving 27 to 28 Injections During¹ Treatment with Sandostatin LAR Depot

Mean Hormone Level	Sandostatin Injection S.C.		Sandostatin LAR Depot	
	n	%	n	%
GH <5.0 ng/mL	69/88	78	73/88	83
<2.5 ng/mL	44/88	50	41/88	47
<1.0 ng/mL	6/88	7	10/88	11
IGF-1 normalized	36/88	41	45/88	51
GH <5.0 ng/mL + IGF-1 normalized	36/88	41	45/88	51
<2.5 ng/mL + IGF-1 normalized	30/88	34	37/88	42
<1.0 ng/mL + IGF-1 normalized	5/88	6	10/88	11

¹Average of monthly levels of GH and IGF-1 over the course of the trials

For the 88 patients in Table 5, a mean GH level of <2.5 ng/mL was observed in 47% receiving Sandostatin LAR Depot. Over the course of the trials, 42% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels.

Table 6 summarizes the data on hormonal control (GH and IGF-1) for those patients in the third clinical trial who received all 12 injections of Sandostatin LAR Depot.

Table 6. Hormonal Response in Acromegalic Patients Receiving 12 Injections During¹ Treatment with Sandostatin LAR Depot

Mean Hormone Level	Sandostatin Injection S.C.		Sandostatin LAR Depot	
	n	%	n	%
GH <5.0 ng/mL	116/122	95	118/122	97
<2.5 ng/mL	84/122	69	80/122	66
<1.0 ng/mL	25/122	21	28/122	23
IGF-1 normalized	82/122	67	82/122	67
GH <5.0 ng/mL + IGF-1 normalized	80/122	66	82/122	67
<2.5 ng/mL + IGF-1 normalized	65/122	53	70/122	57
<1.0 ng/mL + IGF-1 normalized	23/122	19	27/122	22

¹Average of monthly levels of GH and IGF-1 over the course of the trial

For the 122 patients in Table 6, who received all 12 injections in the third trial, a mean GH level of <2.5 ng/mL was observed in 66% receiving Sandostatin LAR Depot. Over the course of the trial, 57% of patients maintained mean growth hormone levels of <2.5 ng/mL and mean normal IGF-1 levels. In comparing the hormonal response in these trials, note that a higher percentage of patients in the third trial suppressed their mean GH to <5 ng/mL on subcutaneous Sandostatin Injection, 95%, compared to 78% across the two previous trials.

In all three trials, GH, IGF-1, and clinical symptoms were similarly controlled on Sandostatin LAR Depot as they had been on Sandostatin Injection.

Of the 25 patients who completed the trials and were partial responders to Sandostatin Injection (GH >5.0 ng/mL but reduced by >50% relative to untreated levels), 1 patient (4%) responded to Sandostatin LAR Depot with a reduction of GH to <2.5 ng/mL and 8 patients (32%) responded with a reduction of GH to <5.0 ng/mL.

Two open-label clinical studies investigated a 48-week treatment with Sandostatin LAR Depot in 143 untreated (de novo) acromegalic patients. The median reduction in tumor volume was 20.6% in Study 1 (49 patients) at 24 weeks and 24.5% in Study 2 (94 patients) at 24 weeks and 36.2% at 48 weeks.

14.2 Carcinoid Syndrome

A 6-month clinical trial of malignant carcinoid syndrome was performed in 93 patients who had previously been shown to be responsive to Sandostatin Injection. 67 patients were randomized at baseline to receive, double-blind, doses of 10 mg, 20 mg or 30 mg Sandostatin LAR Depot every 28 days and 26 patients continued, unblinded, on their previous Sandostatin Injection regimen (100-300 mcg three times daily).

In any given month after steady-state levels of octreotide were reached, approximately 35%-40% of the patients who received Sandostatin LAR Depot required supplemental subcutaneous Sandostatin Injection therapy usually for a few days, to control

exacerbation of carcinoid symptoms. In any given month, the percentage of patients randomized to subcutaneous Sandostatin Injection who required supplemental treatment with an increased dose of Sandostatin Injection was similar to the percentage of patients randomized to Sandostatin LAR Depot. Over the 6-month treatment period, approximately 50%-70% of patients who completed the trial on Sandostatin LAR Depot required subcutaneous Sandostatin Injection supplemental therapy to control exacerbation of carcinoid symptoms although steady-state serum Sandostatin LAR Depot levels had been reached.

Table 7 presents the average number of daily stools and flushing episodes in malignant carcinoid patients.

Table 7. Average No. of Daily Stools and Flushing Episodes in Patients with Malignant Carcinoid Syndrome

Treatment	n	Daily Stools (Average No.)		Daily Flushing Episodes (Average No.)	
		Baseline	Last Visit	Baseline	Last Visit
Sandostatin Injection S.C.	26	3.7	2.6	3.0	0.5
Sandostatin LAR Depot					
10 mg	22	4.6	2.8	3.0	0.9
20 mg	20	4.0	2.1	5.9	0.6
30 mg	24	4.9	2.8	6.1	1.0

Overall, mean daily stool frequency was as well controlled on Sandostatin LAR Depot as on Sandostatin Injection (approximately 2-2.5 stools/day).

Mean daily flushing episodes were similar at all doses of Sandostatin LAR Depot and on Sandostatin Injection (approximately 0.5-1 episode/day).

In a subset of patients with variable severity of disease, median 24 hour urinary 5-HIAA (5-hydroxyindole acetic acid) levels were reduced by 38%-50% in the groups randomized to Sandostatin LAR Depot.

The reductions are within the range reported in the published literature for patients treated with octreotide (about 10%-50%).

78 patients with malignant carcinoid syndrome who had participated in this 6-month trial, subsequently participated in a 12-month extension study in which they received 12 injections of Sandostatin LAR Depot at 4-week intervals. For those who remained in the extension trial, diarrhea and flushing were as well controlled as during the 6-month trial. Because malignant carcinoid disease is progressive, as expected, a number of deaths (8 patients: 10%) occurred due to disease progression or complications from the underlying disease. An additional 22% of patients prematurely discontinued Sandostatin LAR Depot due to disease progression or worsening of carcinoid symptoms.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sandostatin LAR Depot is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits

10 mg kit NDC 0078-0340-61

20 mg kit NDC 0078-0341-61

30 mg kit NDC 0078-0342-61

Demonstration kit NDC 0078-9342-61

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures between 2°C-8°C (36°F-46°F) and protected from light until the time of use. Sandostatin LAR Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

17 PATIENT COUNSELING INFORMATION

Patients with carcinoid tumors and VIPomas should be advised to adhere closely to their scheduled return visits for reinjection in order to minimize exacerbation of symptoms.

Patients with acromegaly should also be urged to adhere to their return visit schedule to help assure steady control of GH and IGF-1 levels.

**Trademark of Thomson Healthcare, Inc.

Sandostatin LAR[®] Depot vials are manufactured by:

Sandoz GmbH, Schaffhausen, Austria

(Subsidiary of Novartis Pharma AG, Basle, Switzerland)

The diluent syringes are manufactured by:

Solvay Pharmaceuticals B.V.

Olst, The Netherlands

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2008-22

© Novartis

PRINCIPAL DISPLAY PANEL

Package Label – 10 mg

Rx Only NDC 0078-0340-61

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

10 mg

For Intragluteal Injection

Contents:

- Vial containing Sandostatin LAR® Depot
- Syringe containing diluent
- Two 1½" 19 gauge needles
- Two alcohol wipes

10mg

For Intragluteal Injection
NDC 0078-0340-61

ATTENTION:

- Follow enclosed instruction booklet precisely
- Use only 1½" 19 gauge needles
- Administer immediately after suspension
- If needle clogs, replace with a new 1½" 19 gauge needle

Incorrect preparation and/or administration could result in failure of drug delivery.



Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)

 **NOVARTIS**



Rx only

10

PRINCIPAL DISPLAY PANEL

Package Label – 20 mg

Rx Only NDC 0078-0341-61

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

20 mg

For Intragluteal Injection

Contents:

- Vial containing Sandostatin LAR® Depot
- Syringe containing diluent
- Two 1½" 19 gauge needles
- Two alcohol wipes

20mg

For Intragluteal Injection
NDC 0078-0341-61

ATTENTION:

- Follow enclosed instruction booklet precisely
- Use only 1½" 19 gauge needles
- Administer immediately after suspension
- If needle clogs, replace with a new 1½" 19 gauge needle

Incorrect preparation and/or administration could result in failure of drug delivery.



Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)

 **NOVARTIS**



Rx only

20

PRINCIPAL DISPLAY PANEL

Package Label – 30 mg

Rx Only NDC 0078-0342-61
Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)
30 mg
For Intragluteal Injection

Contents: • Vial containing Sandostatin LAR® Depot
• Syringe containing diluent
• Two 1½" 19 gauge needles
• Two alcohol wipes

30mg
For Intragluteal Injection
NDC 0078-0342-61

ATTENTION:

- Follow enclosed instruction booklet precisely
 - Use only 1½" 19 gauge needles
 - Administer immediately after suspension
 - If needle clogs, replace with a new 1½" 19 gauge needle
- Incorrect preparation and/or administration could result in failure of drug delivery.



 NOVARTIS



Rx only

30